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May 30, 2000

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Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

00 MAY 31 A10:47

Re: Docket No. 00D-1223
"E11: Clinical Investigation of Medicinal Products in the Pediatric Population"

To Whom It May Concern:

Provided herein are comments of Alcon Research, Ltd. regarding the referenced draft guidance document addressing clinical investigation of medicinal products in the pediatric population.

Section 2.4.2. "*Efficacy*" mentions a few unique features of pediatric studies, but does not address one that is of tremendous importance. That is the uncommon or rare nature of some pediatric diseases. Taking the ophthalmic example of glaucoma, this is important for at least two reasons. First, because the scarcity of these afflicted children translates into small numbers of patients enrolled, the power of statistical tests may be inadequate for **statistically** demonstrating efficacy. Second, again because the children with glaucoma are rare, we do not have the luxury of carefully delineated patient populations as we do with adult studies. We must enroll children with glaucoma that is caused by a variety of conditions. This will of course increase the variability in efficacy results. The FDA should acknowledge in the guidance that these problems exist when studies of rare childhood conditions are undertaken, and appropriately adjust the standard of proof required for demonstration of efficacy

Additionally, there should be a provision for the use of normals in evaluating the safety of drugs in children in those circumstances where the adult disease states for which the drugs are indicated either occur uncommonly, or not at all, in children. In those circumstances, the drugs may have utility as adjunct treatment in children for a pediatric variant of the adult disease such that the availability of these drugs to children would have therapeutic benefit to the child and serve to benefit the community.

Clinical examples in pediatric ophthalmology include:

Bacterial Conjunctivitis in Infants

True bacterial conjunctivitis that is not either ophthalmia neonatorum or dacryostenosis is rare in infants. As such, recruitment for any study intended to support the safety and efficacy of an ophthalmic antibiotic for the treatment of bacterial conjunctivitis in this population would be challenging or perhaps impossible. However, severe ocular infections do occur in this population, making the availability of new antimicrobials vitally important.

Glaucoma in Infants

Glaucoma in infants is generally referred to as Congenital Glaucoma (CG). Its mechanism is very different from that of Chronic Open Angle Glaucoma (COAG); as such, the treatment for CG is very different, and typically involves surgery as the initial intervention. However, topical antiglaucoma agents are used for palliation while awaiting surgery, and do provide limited benefit in some patients. Because CG patents

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generally require very prompt/urgent treatment, pre-surgical CG patients are rare and hard to enroll in studies (CG occurs in our population in 1:10,000 live births). An IRB-approved safety study in normals allowing one eye to be dosed and intraocular pressure (IOP) measured would improve our ability to evaluate drugs originally intended for, and now indicated for the treatment of COAG, for use in an adjunctive fashion in infants.

Besides being addressed in the "*Efficacy*" section of the guidance, the foregoing concerns should be appropriately addressed in Section 2.4.3. "*Safety*" and Section 2.6. "*Ethical Issues in Pediatric Studies*."

Respectfully submitted,

Rebecca G. Walker
Senior Director, Regulatory Compliance

Cc: Stella Robertson, Ph.D.
Bill Fairbairn
Scott Krueger

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